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Resistance to antiplatelet drugs. Can it be assessed?

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SUMMARY

High platelet reactivity (HPR) during dual antiplatelet therapy is a marker of vascular risk, in particular stent thrombosis in patients with acute coronary syndromes. Genetic determinants (CYP2C19*2 polymorphism), advanced age, female gender, diabetes and reduced ventricular function are related to a higher risk to develop HPR. In addition, inflammation and increased platelet turnover, as revealed by the elevated percentage of reticulate platelets in patients' blood that characterize the acute phase of ACS, are associated with HPR. To overcome the limitation of Clopidogrel, new antiplatelet agents (Prasugrel and Ticagrelor) were synthesized and the demonstration of their superiority over Clopidogrel was obtained in two randomized trials TRITON TIMI 38 and PLATO. Due to the current possibility of choosing between multiple antiplatelet strategies, the future prospect is to include the definition of platelet function during treatment in order to set a tailored therapy, in addition to clinical data and classical risk factors.

Speaking of the possible usefulness of platelet aggregation tests in clinical practice means telling a story that began with many question marks and that has arrived at the definition of the existence of platelet hyper-reactivity due to ADP and its potential clinical role [2], in a document of "consensus" [1].

The functionality of platelets can be measured through aggregation induced by various agonists, first of all, the ADP target of thienopyridines and arachidonic acid, which is mainly influenced by the recruitment of acetylsalicylic acid. The "gold standard" method is represented by the aggregation of platelets on platelet-rich plasma. There are also numerous systems, which consent measurement of the aggregation on whole blood, the so-called "point of care" because of its potential usefulness at patient's bedside [3].

First of all, it is essential to define the clinical setting in which the majority of the evidence has been accumulated in this field: the acute phase of patients with acute coronary syndrome undergoing percutaneous revascularization with stent implantation, or the "fate" treatment of the majority of patients with acute coronary syndrome in 2012.

In this clinical context, a considerable number of studies have shown that the presence of ADP platelet hyperreactivity is associated with a significantly increased risk of ischemic events, first of all, of stent thrombosis, myocardial infarction and cardiac death.

Our group has demonstrated this in 804 patients undergoing drug-eluting stent implantation with a 6-month follow-up in the RECLOSE trial [4].

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Confirmation was obtained in a population at particularly high risk such as patients undergoing stenting for unprotected left main coronary artery disease, in which platelet hyperreactivity by ADP was associated with an increased risk of ischemic events in a follow-up of three years [5]. There are also data that have correlated ADP platelet hyperreactivity and events by measuring the platelet hyperreactivity with point of care methods such as Multiplate and Verify-Now [6,7]. These methods appear to be of particular clinical utility because they render the measurement of platelet function possible at the bedside and, potentially, in the cath lab.

More recently, we conducted a prospective cohort study of 1,789 consecutive patients with acute coronary syndrome undergoing percutaneous revascularization procedure in which platelet function was assessed prospectively after clopidogrel loading and the antithrombotic treatment adjusted according to the results of the functional test [8].

Patients with platelet hyperreactivity determined by the presence of platelet aggregation induced by ADP > 70% received an increased dose of clopidogrel or were treated with ticlopidine on the base of the ADP test.

Results have documented that (1) after loading 600 mg of clopidogrel in patients with acute coronary syndrome undergoing invasive procedure, ADP platelet hyperreactivity incidence is relatively low (14%); (2) platelet aggregation remains at high levels (>70%) in 38% of patients after adjustment with first-generation thienopyridine; and (3) platelet hyper-reactivity after clopidogrel loading is associated with an increased risk of ischemic events in short and long term.

What are the possible causes of this ADP platelet hyperreactivity? (Fig. 1). Clopidogrel is a prodrug: only 15% of the administered drug is converted into active metabolites by the cytochrome P4509 enzymes

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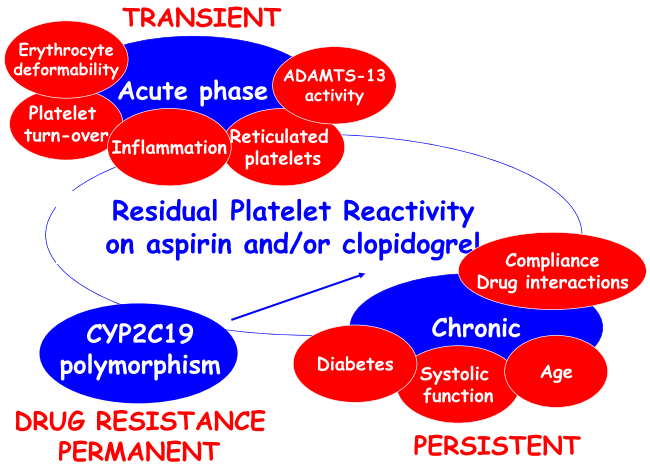

Fig. 1.

(Fig. 2). Researchers have studied possible polymorphisms in the genes encoding these enzymes, and almost contemporaneously, several research groups have shown the role of polymorphism CYP2C19 * 2 in increasing the risk of platelet hyperreactivity and, especially, clinical events [9,10].

Carriers of this polymorphism in heterozygous or homozygous form have an enzyme that works in a reduced manner and, therefore, are at a higher risk of maintaining a persistent platelet reactivity despite treatment. Consequently, carriers of this polymorphism have an increased risk of adverse ischemic events, from stent thrombosis to cardiovascular death. These data were summarized and proven by the more extensive meta-analysis that we published at the end of 2010 [11].

Hence, does genotype really explain the entire association between platelet hyperreactivity and adverse events? The truth in medicine is, as usual, much more complex. We know that the extent of inhibition of platelet function by ADP remains a risk marker of adverse events even within a population that is not carrying the CYP2C19*2 polymorphism and is therefore able to properly metabolize clopidogrel [12].

Possible explanations for this are related to the existence of genetic determinants not yet known, or the presence of other "non-genetic" determinants of hyperreactivity. Advanced age, female sex, diabetes, and reduced left ventricular systolic function are the clinical conditions associated with an increased platelet reactivity and thus to an increased risk of inadequate inhibition of platelet function during standard treatment [13].

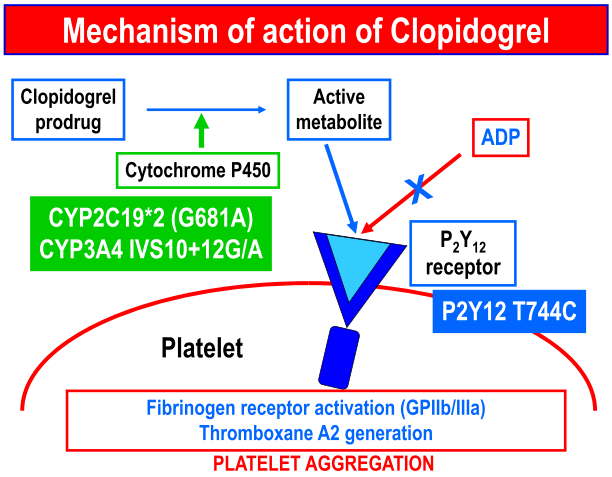

Fig. 2.

The population of diabetic patients with a particularly increased risk of ischemic events is the group which has been most studied: the condition associated with platelet hyperactivity disease explains the increased prevalence of platelet hyperactivity by ADP in this group of patients. It should also be emphasized that the "answer" to aspirin could be modified in this population, and this mechanism has been invoked as a possible explanation for aspirin's lack of effect in reducing cardiovascular events in primary prevention.

There is also a potential interaction between clopidogrel and drugs metabolized by cytochrome P450 [14]. This aspect was revealed for the first time in ex vivo studies, which have shown how omeprazole, the proton pump inhibitor (PPI) most widely used in clinical medicine, is associated with a reduction in the effect of platelet function inhibition induced by ADP-mediated clopidogrel. It was not entirely clear whether this is an effect of the drug or class, since in all clinical trials, the number of patients taking omeprazole is much higher than other PPIs.

Ex vivo studies show that pantoprazole, which follows a different metabolic pathway than other PPIs, does not interfere with the platelet inhibition of clopidogrel [15]. If the effect on platelet function translates into an increased risk of clinical events, it is clear from Hulot's most recent meta-analysis, on the basis of which the intake of PPIs together with clopidogrel significantly increases the risk of ischemic events [16].

A particularly important aspect of the possible existence of acquired determinants of platelet hyperreactivity is the role of the "acute phase": it has been shown how the inflammatory movement and increased platelet turnover that characterize the acute phase of ACS is associated with increased platelet reactivity and an increased risk of hyperreactivity during therapy. We see this clearly when using simple markers of inflammation such as white blood cells and ESR_{14}, as well as through elegant studies showing how cytochemical pro/anti-inflammation balance is all shifted in favor of pro-inflammatory cytokines in patients with platelet hyperreactivity [17].

Moreover, the number of reticulated platelets, the youngest platelets released into the circulation from the marrow and most mRNA content, and which represent a measure of the increased platelet turnover, are higher in patients with platelet hyperreactivity during therapy [18].

Moving from the lab to the individual patient, we can observe the effect of the acute phase even in individual patients: in fact, we have shown that moving away from the acute phase and rechecking our patients after 1 and 6 months, the proportion of patients with significantly decreased platelet hyperreactivity suggests that the shutdown of the movements related to the acute phase significantly reduced the degree of platelet reactivity and therefore the percentage of patients with an inadequate inhibition.

An indirect confirmation of this comes from the results of the CURRENT-OASIS 7 [19] where in the population exposed to PCI, patients randomized to receive a higher dose of clopidogrel in the first week of treatment were those who experienced a significant lower number of ischemic events. This suggests that a more intensive treatment in the acute phase would be able to better protect patients.

What to do with patients presenting platelet hyperreactivity? The first attempt was to intensify therapy with clopidogrel by doubling the dose in pre-prasugrel and pre-ticagrelor eras. This was the attempt tested by the GRAVITAS trial [20], which randomized patients undergoing drug-eluting stent implantation and hyperreactivity demonstrated with Verify Now method to standard treatment of clopidogrel versus doubled dose (150 mg/day). After 6 months, no statistically significant difference was demonstrated between the two treatment groups for ischemic end points. The analysis of data showed that mostly stable patients (60%) were enrolled and only 0.5% of patients with STEMI; therefore, patients who were different from those in which the role of ADP platelet hyperreactivity platelet had been demonstrated.

Furthermore, data concerning the control of platelet function performed at 1 and 6 months demonstrated how, even in the doubled dose group, as many as 40% of patients showed a persistent platelet reactivity that had not been corrected by the adjustment of the

clopidogrel dosage. In support of this finding, the ineffectiveness of intensive treatment was the lack of increase in bleeding between the two groups undergoing treatment. On the other hand, all patients who experienced an ischemic event had higher platelet reactivity that was very close to the chosen hyperreactivity cut-off.

One area of research that still awaits studies in literature is the possible role of platelet hyperreactivity by different agonists, not only ADP but also arachidonic acid and collagen.

In several case studies, but in over 1,000 patients, data of our group [21,22] have shown how global platelet hyperreactivity, both ADP as well as arachidonic acid and collagen, is the true marker of risk of adverse events, identifying the true "aggressive" platelet and "vulnerable" patient requiring personalized treatment.

The perspective is to include the definition of platelet function during treatment in order to better stratify our revascularized SCA patients with stent implantation, in addition to classic risk factors and procedural requirements.

Another fascinating area for future research concerns the most recent data of a possible correlation between excessive inhibition of platelet function during treatment and risk of bleeding. The current and future possibility of choosing between anti-platelet strategies makes policies using the measurement of platelet function, in addition to clinical data as a means of selecting and customizing treatment, even more appropriate.

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